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Enclosed herewith:

1) **Communication**
2) **Papers originally faxed to the PTO on January 22, 2002**

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DOCKET NO.: ISIS-3105 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Teng and Hardee

OFFICIAL

Serial No.: **09/108,673** Group Art Unit: **1636**

Filed: **July 1, 1998** Examiner: **W. Sandals**

For: **COMPOSITIONS AND METHODS FOR THE DELIVERY OF OLIGONUCLEOTIDES VIA THE ALIMENTARY CANAL**

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On June 6, 2002

Paul K. Legaard Reg. No 38,534

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

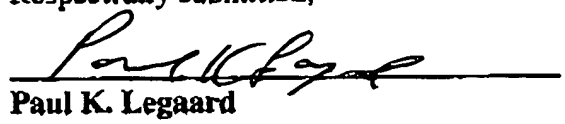
COMMUNICATION

Examiner Sandals indicated in a telephone conversation on June 6, 2002 that the Amendment and Request for Reconsideration that was filed via facsimile on January 22, 2002 was not received. Examiner Sandals indicated, however, that the Declaration of Dr. Teng, which was also filed via the same facsimile on January 22, 2002 was, in fact, received. Accordingly, pursuant to the request of Examiner Sandals, attached hereto is a copy of the facsimile cover sheet, Amendment and Request for Reconsideration, Amendment Transmittal Letter, Declaration of Dr. Teng, Exhibit A, and the confirmation report of the facsimile transmission associated with the January 22, 2002 facsimile transmission.

DOCKET NO.: ISIS-3105 **PATENT**

The Examiner is invited to call Applicants' undersigned representative at (215) 564-8906 if he has any questions regarding this matter.

Respectfully submitted,



Paul K. Legaard
Registration No. **38,534**

Date: **June 6, 2002**

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DOCKET NO.: ISIS-3105 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
Teng and Hardee

Serial No.: 09/108,673 **Group Art Unit:** 1636

Filing Date: July 1, 1998 **Examiner:** W. Sandals

For: COMPOSITIONS AND METHODS FOR THE DELIVERY OF OLIGONUCLEOTIDES VIA THE ALIMENTARY CANAL

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On 22 JANUARY 2002

Paul K. Legaard

Paul K. Legaard Reg. No. 38,534

Box ☐ NON-FEE

☐ AF

Assistant Commissioner for Patents
Washington DC 20231

Sir:

AMENDMENT TRANSMITTAL LETTER

Transmitted herewith for filing in the above-identified patent application is:

☐ A Preliminary Amendment.

☒ An Amendment and Request for Reconsideration Responsive to the Office Action Dated October 23, 2001.

☐ An Amendment Supplemental to the Paper filed _____.

☐ Other: _____.

☒ Applicant(s) has previously claimed small entity status under 37 CFR §1.27.

☐ Applicant(s) by its/their undersigned attorney, claims small entity status under 37 CFR §1.27 as:

- ☐ an Independent Inventor
- ☐ a Small Business Concern
- ☐ a Nonprofit Organization

☐ This application is no longer entitled to small entity status. It is requested that this be noted in the files of the Patent and Trademark Office.

☐ Substitute Pages _____ of the Specification are enclosed.

☐ An Abstract is enclosed.

☐ _____ Sheets of Proposed Corrected Drawings are enclosed.

☐ A Certified Copy of each of the following applications: _____ _____ is enclosed.

☐ An Associate Power of Attorney is enclosed.

☐ Information Disclosure Statement.

- ☐ Attached Form 1449.
- ☐ A copy of each reference as listed on the attached Form PTO-1449 is enclosed herewith.

☐ Appended Material as follows: _____.

☒ Other Material as follows: Declaration Pursuant to 37 CFR §1.132.

FEE CALCULATION

☐ No Additional Fee is Due.

	REMAINING AFTER AMENDMENT	HIGHEST PAID FOR	EXTRA	SMALL ENTITY RATE	SMALL ENTITY FEE	NOT SMALL ENTITY RATE	NOT SMALL ENTITY FEE
TOTAL CLAIMS	37	42 (20 MINIMUM)	0	$9 EACH	$0	$18 EACH	$
INDEP. CLAIMS	4	4 (3 MINIMUM)	0	$42 EACH	$0	$84 EACH	$
FIRST PRESENTATION OF MULTIPLE DEPENDENT				$140	$0	$280	$
☐ ONE MONTH EXTENSION OF TIME				$55	$0	$110	$
☐ TWO MONTH EXTENSION OF TIME				$200	$0	$400	$
☐ THREE MONTH EXTENSION OF TIME				$460	$0	$920	$
☐ FOUR MONTH EXTENSION OF TIME				$720	$0	$1440	$
☐ FIVE MONTH EXTENSION OF TIME				$980	$0	$1960	$
☐ LESS ANY EXTENSION FEE ALREADY PAID				minus	($ 0)	minus	($)
☐ TERMINAL DISCLAIMER				$55	$0	$110	$
☐ OTHER FEE OR SURCHARGE AS FOLLOWS:					0		
TOTAL FEE DUE					$0		$

☐ A Check is Enclosed in the Foregoing Amount Due.

☐ Petition is hereby made under 37 C.F.R. 1.136(a) to extend the time for response to the Office Action of @@ to and through @@ comprising an extension of the shortened statutory period of @@ month(s).

☒ The Commissioner is hereby requested to grant an extension of time for the appropriate length of time, should one be necessary, in connection with this filing or any future filing submitted to the U.S. Patent and Trademark Office in the above-identified application during the pendency of this application. The Commissioner is further authorized to charge any fees related to any such extension of time to deposit account 23-3050. This sheet is provided in duplicate.

☒ The Commissioner is authorized to charge payment of the following fees and to refund any overpayment associated with this communication or during the pendency of this application to deposit account 23-3050. This sheet is provided in duplicate.

☐ The Foregoing Amount Due for Filing this Paper.

☒ Any additional filing fees required, including fees for the presentation of extra claims under 37 C.F.R. 1.16.

☒ Any additional patent application processing fees under 37 C.F.R. 1.17 or 1.20(d).

SHOULD ANY DEFICIENCIES APPEAR with respect to this application, including deficiencies in payment of fees, missing parts of the application or otherwise, the United States Patent and Trademark Office is respectfully requested to promptly notify the undersigned.

Date: 22 JANUARY 2002

Paul K. Legaard
Registration No. 38,534

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DOCKET NO.: ISIS-3105 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Teng and Hardee

Serial No.: **09/108,673** Group Art Unit: **1636**

Filed: **July 1, 1998** Examiner: **W. Sandals**

For: **COMPOSITIONS AND METHODS FOR THE DELIVERY OF OLIGONUCLEOTIDES VIA THE ALIMENTARY CANAL**

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On January 22, 2002

Paul K. Legaard Reg. No. 38,634

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

AMENDMENT AND REQUEST FOR RECONSIDERATION

In response to the Office Action mailed October 23, 2001, Applicants respectfully request that the application be amended as follows.

In the Claims:

Please cancel claims 40, 56, and 78, amend claims 25, 50, 54, 61, 63, 64, 66, 74, 76 and 80, and add new claim 82 to read as follows:

25. (Amended four times) A method of enhancing penetration of an antisense nucleic acid across the alimentary canal of an animal comprising administering to said animal the composition of claim 44, wherein said composition enhances penetration of said nucleic acid across the alimentary canal of said animal.

50. (Amended) The composition of claim 49 wherein said antisense oligonucleotide decreases the expression of a cellular adhesion protein or the rate of cellular proliferation.

54. (Amended) The composition of claim 44 wherein said composition is propylene glycol based.

61. (Amended twice) A composition comprising a nucleic acid and capric acid or lauric acid or a pharmaceutically acceptable salt thereof, wherein said nucleic acid has a modified nucleobase or a modified sugar residue.

63. (Amended) The composition of claim 62 wherein said antisense oligonucleotide decreases the expression of a cellular adhesion protein or the rate of cellular proliferation.

64. (Amended) The composition of claim 61 wherein said nucleic acid has a cytosine to 5-methyl-cytosine substitution or a 2'-methoxyethoxy modification.

66. (Amended) A method of delivering an antisense nucleic acid to the intestinal mucosa comprising contacting the alimentary canal with a composition comprising a nucleic acid and at least two fatty acids, or pharmaceutically acceptable salts thereof, wherein said nucleic acid has at least one chemical modification selected from the group consisting of a cytosine to 5-methyl-cytosine substitution, a phosphorothioate linkage and a 2'-methoxyethoxy modification.

74. (Amended) The method of claim 73 wherein said antisense oligonucleotide decreases the expression of a cellular adhesion protein or the rate of cellular proliferation.

76. (Amended) The method of claim 66 wherein said composition is propylene glycol based

80. (Amended) The method of claim 66 wherein said composition further comprises a bile salt.

82. (New claim) A method of delivering an antisense nucleic acid to the intestinal mucosa comprising contacting the alimentary canal with a composition comprising a nucleic acid and capric acid or lauric acid or a pharmaceutically acceptable salt thereof, wherein said nucleic acid has a cytosine to 5-methyl-cytosine substitution or a 2'-methoxyethoxy modification.

REMARKS

Claims 25-27, 40, 44-50, 53-64 and 66-81 are stated by the Examiner to be pending in the present application. As a preliminary matter, however, in the response filed August 14, 2001, Applicants cancelled claims 40, 56, and 78, amended claims 25, 50, 54, 61, 63, 64, 66, 74, 76 and 80, and added new claim 82. None of these amendments appear to have been entered. Accordingly, Applicants have, again, amended the claims in an identical manner. Upon entry of the present Amendment, claims 25-27, 44-50, 53-55, 57-64, 66-77, and 79-82 will be pending.

Applicants acknowledge receipt of the "Attachment for PTO-948" outlining changes for prosecution of applications containing drawings. The present application, however contains no drawings. Accordingly, the "Attachment for PTO-948" is not relevant in the present application.

The Office Action points out the typographical error in reciting "proylene" in claims 54 and 76. Applicants have previously corrected the typographical error in claims 54 and 76 in the response filed August 14, 2001. To the extent that such amendment has not, in fact, been entered as requested, Applicants again make the amendments herein.

I. The Claimed Inventions Are Not Obvious

Claims 44-50 and 53-64 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the combination of WO 97/05903 (hereinafter, the "Watts reference") in view of U.S. Patent No. 5,994,062 (hereinafter, the "Mulshine reference") and U.S. Patent No. 5,707,648 (hereinafter, the "Yiv reference"). The Office Action asserts that it would have been obvious to combine the composition of the Watts reference with the method of delivery of the Mulshine reference. The Office Action also asserts that it would have been further obvious modify the composition of the Watts reference by the addition of a fatty acid from the Yiv reference. Applicants

traverse the rejection and request reconsideration thereof because the reasons identified in the Office Action for motivation to combine the cited references are merely conclusory statements of the Examiner.

As a preliminary matter, Applicants take this opportunity to, again, correct the Examiner's continued misinterpretation of the Watts reference. The Office Action asserts at page 9 that the Watts reference teaches a "composition comprising a nucleic acid and a mixture of fatty acids." As pointed out during the interview with the Examiner and in the previously filed response, ***this is not true***! Rather, the Watts reference reports a drug in combination with a mixture "of a fatty acid having 6 to 16 carbon atoms or related mono/diglycerides and a pharmaceutically acceptable dispersing agent" (emphasis added) (see, page 5 of the Watts reference). Subsequent discussions with the Examiner resulted in an agreement that mono/diglycerides of fatty acids were not the same as the fatty acids themselves. Thus, the Watts reference does not teach or suggest the combination of a nucleic acid and at least two fatty acids as recited in claim 44 or the combination of a nucleic acid and capric acid or lauric acid having the modifications recited in claim 61. Noticeably absent from the Office Action is any citation that supports any of the assertions in the Office Action.

The only motivation for combining the Watts, Mulshine and Yiv references is the following text found at pages 10-11 of the Office Action:

> The combination of fatty acids taught by each of WO 97/05903 [the Watts reference] and US 5,707,648 [the Yiv reference] make obvious the combination of two or more fatty acids in a composition as taught in the instant claimed composition and methods, since it is obvious to combine the teachings of two compositions and methods to make a third composition which is merely the combination of the two compositions, namely, two or more fatty acids in the instant composition.

This conclusory statement amounts asserts that it is obvious to combine two compositions into a third composition because the third composition is the combination of the two compositions. This circular reasoning is wholly insufficient to establish the level of motivation to make out a *prima facie* case of obviousness. A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." *In re*

Kotzab, 217 F.3d 1365, 1369, 55 U.S.P.Q.2d 1313, 1316 (Fed. Cir. 2000). "The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time." *In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999) (quoting *Interconnect Planning Corp. v. Feil*, 774 F. 2d 1132, 1138, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985). To establish a *prima facie* case of obviousness, "there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant." *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998). "In other words, the examiner must show reasons that the skilled artisan, confronted with the same problem as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *In re Rouffet*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1458 (Fed. Cir. 1998). In no way can the circular reasoning provided in the Office Action suffice to establish the requisite level of motivation to combine the cited references to produce Applicants' claimed compositions.

In view of the lack of any credible reasons for motivation to combine the cited references, it is quite clear that the only motivation for combining the references in the manner suggested in the Office Action comes from Applicants' specification. Applicants note that "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). Under this standard, none of the prior art of record, alone or in any proper combination, discloses or suggests the present invention as defined by the amended claims. This is not to say that it is impossible to combine selected elements of several references to show the obviousness of an invention, however, there still must be a "suggestion or motivation in the prior art to make the selection." *In re Gorman*, 18 U.S.P.Q.2d 1885, 1888 (Fed. Cir. 1991) (claim held obvious in view of combined teachings of references showing elements for same purpose as claimed invention).

To the extent that the Examiner continues to carry forward the present obviousness rejection, Applicants again point out that the present specification provides unexpected and surprising results. In Example 3 of the specification, Formulation 1 (lauric acid; C12) and

Formulation 2 (capric acid; C10) each, alone, resulted in 5% absorption. When lauric acid and capric acid were combined in Formulation 3, however, absorption increased unexpectedly to 15%, which clearly indicates a synergistic effect. It is well-settled that evidence of unobvious or unexpected advantageous properties can be presented to rebut a *prima facie* case of obviousness. *In re Chupp*, 816 F.2d 643, 645, 2 U.S.P.Q.2d 1437, 1439 (Fed. Cir. 1987). Further, Applicants provide herewith a Declaration under 37 C.F.R. § 1.132 of Dr. Teng, a co-inventor of the present application. In his Declaration, Dr. Teng states that an experiment was performed along the lines of the experiment described in Example 4 of the present application. Rat jejunum, however, was used instead of rat ileum. Rats that were administered a composition comprising caprylic acid (C8) yielded 0.9% absorption and rats administered a composition comprising lauric acid (C12) yielded 8.3% absorption. Rats administered a composition comprising both caprylic acid and lauric acid, however, yielded 11% absorption. Dr. Teng asserts that such a combination produced a result greater than would have been expected in view of the individual absorptions obtained. Thus, Applicants have provided ample unexpected and surprising results.

Thus, the claimed compositions comprising at least two fatty acids are not obvious in view of the combination of cited references. First, the Office Action fails to provide sufficient motivation for combining the teachings of the Watts, Mulshine and Yiv references. Second, Applicants provide unexpected and surprising results. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

II. The Claims Are Clear And Definite

Claims 25-27, 56, 64, 78 and 80 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being vague and indefinite. Applicants traverse the rejection and respectfully request reconsideration in view of the amended claims.

As a preliminary matter, each of these rejections has, in fact, been addressed in Applicants' response dated August 14, 2001. They are repeated here for the sake of completeness.

The Office Action asserts that claim 25 is missing an essential step in that the claim allegedly fails to recite a step for administering the composition to the alimentary canal. As pointed

out during the interview and in the previously filed response, however, claim 25 recites "A method ...comprising **administering**..." (emphasis added). Thus, the step of "administering" is, indeed, recited in claim 25. Thus, claim 25 is definite within the meaning of § 112. *In re Mercier*, 185 U.S.P.Q. 774 (C.C.P.A. 1975) (claims sufficiently define an invention so long as one skilled in the art can determine what subject matter is or is not within the scope of the claims).

The Office Action asserts that the breadth of the ranges of the modifications recited in claims 61 and 64 are considered indefinite. Applicants have amended claims 61 and 64 in the previously filed response, as recommended during the interview. Thus, the range of modifications recited in claim 64 falls within the scope of the range of modifications recited in claim 61. To the extent that the amendments to claims 61 and 64 have not been entered, they are made herein again.

Claim 66 has been amended in the previously filed response as suggested during the interview to replace the term "oligonucleotide" with the phrase "nucleic acid" to more properly provide antecedent basis. To the extent that the amendment to claim 66 has not been entered, it is made herein again.

The Office Action asserts that claims 56 and 78 lack antecedent basis for the phrase "when administered to an animal." Claims 56 and 78 have, in fact, been cancelled.

In addition, claim 80 has been amended again, as suggested in the Office Action, to insert the term "further." No change in claim scope has been effected.

In view of the comments and amendments to the claims, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

III. The Claimed Inventions Are Enabled

Claims 25-27, 40 and 66-81 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to enable the full scope of the claimed invention. Applicants traverse the rejection and request reconsideration thereof because one skilled in the art would be able to practice the claimed inventions without being required to perform undue experimentation.

The Office Action asserts at page 6:

> Enablement for the full scope of the specification is required for enablement of the claims as written, and claims which recite the use of a nucleic acid must be enabled for all of the stated uses of the nucleic acid.

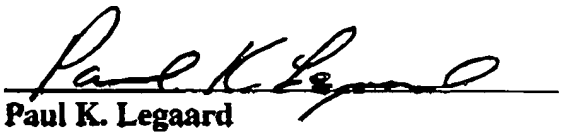
The Office Action concludes that because Applicants' specification mentions gene therapy, and gene therapy is allegedly not enabled, the claims are not enabled. Noticeably absent in the Office Action, however, is any citation of case law supporting this interpretation of the enablement requirement of 35 U.S.C. §112, first paragraph. Indeed, ***Applicants are only required to enable the claimed inventions***. In applying the enablement requirement, ***the "invention" that must be enabled is that defined by the claims***. *Ex parte Erlich*, 3 U.S.P.Q.2d 1011 (Pat. Off. Bd. App. 1987). The Examiner is reminded that claim 25 is directed to methods of "enhancing penetration of an antisense nucleic acid across the alimentary canal of an animal" and that claims 66 and 82 are directed to methods of "delivering an antisense nucleic acid to the intestinal mucosa."

Applicants' specification amply enables the claimed methods. The Declaration of Dr. Hardee and Dr. Teng showed that the claimed pharmaceutical compositions, in fact, enhance penetration of a nucleic acid across the alimentary canal of an animal. Paragraphs 3-5 of the Declaration describe experiments whereby penetration of an oligonucleotide across the alimentary canal of rats and dogs is enhanced by delivery of the oligonucleotide along with at least two fatty acids. Such examples are also set forth in Applicants' specification in Examples 3, 4 and 13. Indeed, the Office Action acknowledges that the specification "does provide teaching on the introduction of nucleic acids into the blood and generally into the organs of an animal via the enteral pathway" (see, page 3 of the Office Action). Thus, Applicants have amply enabled the claimed inventions. Further, one skilled in the art is not required to perform, and Applicants are not required to enable, gene therapy to practice the claimed inventions. Thus, no amount of undue experimentation is required to practice Applicants' claimed inventions. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

IV. Conclusion

It is respectfully submitted that this application is now in condition for allowance. Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,



Paul K. Legaard
Registration No. **38,534**

Date: **January 22, 2002**

WOODCOCK WASHBURN LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103
Telephone: (215) 568-3100
Facsimile: (215) 568-3439

DOCKET NO.: ISIS-3105 **PATENT**

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 40, 56, and 78 have been cancelled.

Claim 82 has been added.

Claims 25, 50, 54, 61, 63, 64, 66, 74, 76 and 80 have been amended as follows:

25. (Amended four times) A method of enhancing penetration of [a] an antisense nucleic acid across the alimentary canal of an animal comprising administering to said animal the composition of claim 44, wherein said composition enhances penetration of said nucleic acid across the alimentary canal of said animal.

50. (Amended) The composition of claim 49 wherein said antisense oligonucleotide [modulates] decreases the expression of a cellular adhesion protein or the rate of cellular proliferation.

54. (Amended) The composition of claim 44 wherein said composition is [proylene] propylene glycol based.

61. (Amended twice) A composition comprising a nucleic acid and capric acid or lauric acid or a pharmaceutically acceptable salt thereof, wherein said nucleic acid has [at least one chemical modification selected from the group consisting of a cytosine to 5-methyl-cytosine substitution, a phosphorothioate linkage and a 2'-methoxyethoxy modification] a modified nucleobase or a modified sugar residue.

63. (Amended) The composition of claim 62 wherein said antisense oligonucleotide [modulates] decreases the expression of a cellular adhesion protein or the rate of cellular proliferation.

64. (Amended) The composition of claim 61 wherein said nucleic acid has [at least one chemical modification selected from the group consisting of a modified nucleobase, a modified sugar residue, and a modified backbone linkage] a cytosine to 5-methyl-cytosine substitution or a 2'-methoxyethoxy modification.

66. (Amended) A method of delivering [a] an antisense nucleic acid to the intestinal mucosa comprising contacting the alimentary canal with a composition comprising a nucleic acid and at least two fatty acids, or pharmaceutically acceptable salts thereof, wherein said [oligonucleotide] nucleic acid has at least one chemical modification selected from the group consisting of a cytosine to 5-methyl-cytosine substitution, a phosphorothioate linkage and a 2'-methoxyethoxy modification.

74. (Amended) The method of claim 73 wherein said antisense oligonucleotide [modulates] decreases the expression of a cellular adhesion protein or the rate of cellular proliferation.

76. (Amended) The method of claim 66 wherein said composition is [proylene] propylene glycol based.

80. (Amended) The method of claim 66 wherein said composition further comprises a bile salt.

82. (New claim) A method of delivering an antisense nucleic acid to the intestinal mucosa comprising contacting the alimentary canal with a composition comprising a nucleic acid and capric acid or lauric acid or a pharmaceutically acceptable salt thereof, wherein said nucleic acid has a cytosine to 5-methyl-cytosine substitution or a 2'-methoxyethoxy modification.

DOCKET NO.: ISIS-3105 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Teng and Hardee

Serial No.: **09/108,673** Group Art Unit: **1636**

Filed: **July 1, 1998** Examiner: **W. Sandals**

For: **COMPOSITIONS AND METHODS FOR THE DELIVERY OF OLIGONUCLEOTIDES VIA THE ALIMENTARY CANAL**

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

I, Ching-Leou C. Teng, Ph.D., do hereby declare as follows:

1. I am currently an Assistant Director of Drug Delivery Research and Pharmaceutical Development at Isis Pharmaceuticals, Inc. ("Isis") in Carlsbad, California. My responsibilities include the following: conducting preformulation and formulation for new oligonucleotide drugs, performing formulation research to improve existing formulations or alter the route of administration; designing and conducting validation studies and published technique reports for the chemistry, manufacturing, and controls (CMC) and microbiology sections of new drug applications (NDA); participating in the preparation of the CMC section for investigational new drug (IND) and NDA submissions; coordinating the drug product fill in-house and contract manufacturer for pre-clinical and clinical studies; and animal model development for penetration enhancer screening and formulation evaluation of oligonucleotide via oral administration. I have a Ph.D. in pharmaceutics and have worked in this field for more than 25 years. My *curriculum vitae* is attached hereto as Exhibit A.

2. From 1992 to 1998, I was a Senior Scientist in drug Discovery Research and Pharmaceutical Development at Isis, where my responsibilities were also as listed above.

3. From 1988 to 1992, I was a Reviewer in the Pharmacokinetics Evaluation Branch, Division of Pharmaceutics, Food and Drug Administration (FDA), Rockville, Maryland.

4. From 1986 to 1988, I was a Postdoctoral Research Fellow in the college of Pharmacy at the University of Michigan My research focused on the development of a reactor to remove heparin in extracorporeal circulation.

5 From 1981 to 1986, I was a graduate student in the College of Pharmaceutics at the University of Michigan. I received my Ph.D. in 1986, and my dissertation was entitled "Kinetics of adhesion of polymer-coated particles to intestinal mucous surfaces."

6. From 1978 to 1981, I was a Chemist in the Pharmacokinetic Drug analysis Laboratory, Veterans Administration Hospital, Fargo, North Dakota I obtained my Master's degree in Pharmaceutical Science from North Dakota State University.

7. From 1974 to 1978, I was a Registered Pharmacist, Pharmacy Department, Mackay Memorial Hospital, Taipei, Taiwan. I received my Bachelor of Science degree in 1974 from Taipei Medical College.

8. I am a co-inventor of the above-referenced patent application along with Greg Hardee.

9. *In situ* perfusion studies were performed using the sodium salts of caprylic (C8) and lauric (C12) acid essentially as described in Example 4 of the specification of the above-referenced application, except that rat jejunum was used instead of rat ileum. Six rats were administered C8 only (1% w/v), three were administered C12 only (1% w/v), and three were administered a combination of C8 and C12 (0.5% each, w/v). The average individual absorptions

for C8 and C12 were 0.9%, and 8.3%, respectively. The combination of C8 and C12, however, resulted in an absorption of 11%. This combination of C8 and C12 produced a result greater than would have been expected in view of the individual absorptions obtained.

10. I declare that all statements made herein are of my own knowledge true and statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Ching-Leou Teng

Ching-Leou C. Teng, Ph.D.

Jan 18, 2002

Date

Ching-Leou C. Teng, Ph.D.

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ACADEMIC SUMMARY:

1986-1988 Postdoctoral Research Fellow.
College of Pharmacy, The University of Michigan
Research focused on the development of a reactor to remove heparin in extracoporeal circulation. Advisor, Dr. Victor Yang.

1981-1986 Ph.D. in Pharmaceutics.
College of Pharmacy, The university of Michigan.
Dissertation: Kinetics of adhesion of polymer-coated particles to intestinal mucous surface. Advisor, Dr. Norman F. H. Ho.

1978-1981 M.S. in Pharmaceutical Science.
College of Pharmacy, North Dakota State University.
Thesis: I: Cd/Sephadex interaction
II: Cd biological uptake
Advisor, Dr. Fred F. Farris.

1970-1974 B.S. in Pharmacy.
Taipei Medical College, Taiwan.

EXPERIENCES:

March 1992-Present: ISIS Pharmaceuticals, Carlsbad, CA

April 1998 Assistant Director, DDR&PD
March 1992 Senior Scientist, Drug Delivery Research and Pharmaceutical Development (DDR&PD)

1. Conducted preformulation and formulation studies for new drug entities
   - Intraocular injection – carried out from pre-clinical to market
   - Intravenous injection – phase III
   - Enema – phase II
   - Solid formulation – pre-clinical
2. Performed formulation research to improve the existing formulation or alter the administration route
   - Controlled release formulation for subcutaneous injection
   - Transdermal drug delivery
   - Microemulsion for oral delivery
2. Designed and conducted validation studies and published technique reports for the CMC and microbiology sections of NDA
3. Participated in the preparation of CMC section for IND and NDA submissions
4. Coordinated the drug product fill in house and contract manufacturer for pre-clinical and clinical studies
5. Animal model development for enhancer screening and formulation evaluation of oligonucleotide via oral administration

1988-1992: Food and Drug Administration, Rockville, Maryland
Reviewer, Pharmacokinetics Evaluation Branch, Division of Biopharmaceutics,

1. Reviewed IND and NDA submissions of cardio-renal and gastrointestinal drug products and recommended the approval of the biopharmaceutic section to the New Drug Evaluation Divisions.
2. Designed and evaluated protocols for pharmacokinetics, bioequivalence and dose proportionality studies
3. Consulted Pharmaceutical industries regarding scientific and regulatory issues.
4. Advised medical officers, pharmacologists and chemists on scientific and regulatory issues concerning new drug applications.
5. Represented the Division of Biopharmaceutics in the preparation of stereoisomer guidelines.
6. Conducted mathematic modeling to understand the pharmacokinetic of enterohepatic circulation drugs (ursodeoxycholic acid)

1978-1981: Veterans Administration Hospital, Fargo, North Dakota
Chemist, Pharmacokinetic Drug Analysis Laboratory

1974-1978: Mackay Memorial Hospital, Taipei, Taiwan
Registered Pharmacist, Pharmacy Department,

PUBLICATIONS:

1. S. M. Johnson, C. Chan, S. Cheng, J. L. Shimek, G. Nygard, and S. K. Wahba Khalil, "Isocratic High-Performance Liquid Chromatographic Method for the Determination of tricyclic Antidepressants and Metabolites in Plasma" J. Pharm. Sci., 71, 1027, (1982).

1. C. L. C. Teng and N. F. H. Ho, "Mechanistic Studies in the Simultaneous Flow and adsorption of Polymer-Coated Latex Particles on Intestinal Mucus I: Methods and Physical Development "J. Controlled Release, 6, 133, (1987).

2. Ching-Leou C. Teng, Jae-Seung Kim, Friedrich K. Port, Thomas W. Wakefield, Gerd O. Till, and Victor C. Yang, "a Protamine Filter For Extracorporeal Blood Heparin Removal" American Society of Artificial and Internal Organs Transactions, 34, 743-746 (1988).

3. Victor C. Yang and Ching-Leou Teng, "A Protein-Bound Polymeric Filter Device for Extracorporeal Blood Deheparinization" Polymeric Materials Science and Engineering, 58, 116-119 (1988).

4. Ching-Leou C. Teng and Victor C. Yang, "A Facile Colormetric Protamine Titration Method" J. of Laboratory and Clinical Medicine, 43, 498-504, (1989).

5. Jae-Seung Kim, Christopher Vincent, Ching-Leou C. Teng, Thomas W. Wakefield, and Victor C. Yang, "A Novel Approach to Anticoagulation Control" American Society for Artificial Internal Organs Transactions, 35, 644-646, (1989).

6. You-Yin Fu, Ching-Leou C. Teng, and Victor C. Yang, "Rapid and Precise Whole Blood Protamine Titration" American Society of Artificial and Internal Organs Transactions, 36, M660-663, (1990).

7. Victor C. Yang and Ching-Leou C. Teng, "An Immobilized Protamine System for Removing Heparin in Extracorporeal Blood Circulation' Biomimetic Polymers, Plenum Press, 175-190 (1990).

8. Victor C. Yang, Ching-Leou C. Teng, and Jae-Seung Kim, "A Filter for the Prevention of both Heparin and Protamine Induced Complications Associate with Extracorporeal Therapy" Biomedical Instrumentation and Technology, 24, 433-439 (1990).

9. Victor C. Young, Friedrich K. Port, Ching-Leou C. Teng, Jae-Seung Kim, Gerd O. Till, and Thomas W. Wakefield, "The use of Immobilized Protamine in Removing Heparin and Preventing Protamine Induced Complexes During the Extracorporeal Blood Circulation" Anesthesiology, 75:288-297 (1991).

10. Victor C. Yang, You-Yin Fu, and Ching-Leou C. Teng, "A Method for the Quantitation of Protamine in Blood" Thrombosis Research , 74, 427-434 (1994).

11. Bennett, F.C, Butler, M., Cook, P.D., Geary, R., Levin, A., Mehta, R., Teng, C-L., Deshmukh, H.M., Tillman, L. and Hardee, G.E. Antisense oligonucleotides based therapeutics. In:Templeton, N.S and Lasic, D.D, eds. Gene Therapy. Marcel Dekker, Inc. 2000:305-332.

12. S. Kevin Li, Abdel-Halim Ghanem, Ching-Leou Teng, Gregory E. Hardee, and William I. Higuchi, "Iontophoretic Transport of Oligonucleotide Across Human Epidermal Membrane:a study of the NERNST-PLANCK model" J. Pharm. Sci. 90, 915-931 (2001)

13. WeiQi Lin, Michel Cormier, Ahmad Samiee, Angie Griffin, Bonny Johnson, Ching-leou Teng, Gregory E Hardee, and Peter E Daddona, "Transdermal Delivery of Antisense Oligonucleotide with Macroflux Microprojection Patch Technology" Pharm. Res. In Print

PATENTS

1. Teng, Ching-Leou; Cook, Philip D.; Tillman, Lloyd; Hardee, Gregory E.; Ecker, David J.; Manoharan, Muthiah. Compositions and methods for non-parenteral delivery of oligonucleotides. Application: WO 9960012 A1 19991125.

2. Teng, Ching-Leou; Hardee, Greg. Compositions and methods for the oral delivery of antisense oligonucleotide via alimentary canal. Application: WO 9901579 A1 19990114.

3. Hardee, Gregory E.; Tillman. Lloyd G.; Mehta, Rahul C.; Teng. Ching-Leou. Multiparticulate formulations containing polycationic complexes. Application: WO 0050050 A1 20000831